Joint Bone Spine 90 (2023) 105605

Contents lists available at ScienceDirect

Joint Bone Spine

journal homepage: www.elsevier.com

Letter to the Editor

Comparing COVID-19 disease severity in patients with rheumatic and inflammatory diseases between the first and the subsequent waves

ARTICLE INFO

Keywords:
COVID-19 update
Rheumatic disorders
Connective tissue diseases
Vasculitis
Systemic auto-inflammatory diseases
Rituximab

Eight waves of the COVID-19 pandemic have occurred from spring 2020 to early 2023 [1]. It remains controversial whether patients with iRMD are at increased risk of SARS-CoV-2 infection and mortality [2,3]. This study is an update to our observational, multicenter, French national cohort study in patients with confirmed iRMD [4]. The objective is to determine whether COVID-19 disease severity and associated predictors differed from March 2020 to July 06, 2020 (first wave of COVID-19) with iRMD patients enrolled between July 06, 2020 and September 2021 (second, third, and fourth waves of COVID-19). All eligible patients/representatives were informed, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Additional study details are in the Supplemental Methods (Doc S1).

We evaluated COVID-19 severity in 1973 patients with confirmed COVID-19. Clinical characteristics are in Tables S1–S3, and were similar between pandemic waves. Associations between clinical characteristics, demographics, and rheumatic disease treatments with COVID-19 disease severity were not different according to COVID-19 waves (Tables S4 and S5, interaction *P*-values > 0.05).

As previously [4], age and being female were identified as drivers of disease severity (Table S6). Age- and sex-adjusted analyses identified iRMD patients with traditional cardiovascular disease (CVD) comorbidities and auto-inflammatory diseases (aOR = 3.09, 95% CI: 0.97–8.48) as more likely to develop severe disease than those with chronic inflammatory arthritis disease. Inflammatory disease activity was not associated with frequency of COVID-19 severity. Use of corticosteroids (aOR = 3.00, 95% CI: 2.20–4.09) and rituximab (aOR = 3.45, 95% CI: 2.14–5.55) was associated with severe disease, while use of the biologic TNFα blocker (aOR = 0.29, 95% CI: 0.17–0.48) was predictive of less severe disease (Table S7).

Death was more frequent in older patients (aOR [≥ 75] = 59.88, 95% CI: 25.65–139.76), patients with CVD comorbidities (*P* < 0.05 for all), and cancer (aOR = 2.21, 95% CI: [1.09–4.47] Table S8). Evaluation of iRMD treatments and survival yielded results comparable to our first report (Table S9) [4]. Use of mycophenolate mofetil (aOR = 10.17, 95% CI: 3.37–30.66) was strongly associated with death, and TNFα blocker use (aOR = 0.28, 95% CI: 0.12–0.66)

Table 1
Multivariable analyses for disease severity.

Variable	Imputed analysis[a] (*n* = 1973)		Available case analysis (*n* = 1771)	
	n/N	OR [95%CI]	*n*/N	OR [95%CI]
Age (years)	222/1973	1.05 (1.03 to 1.07)*	199/1771	1.05 (1.03 to 1.06)*
Female gender	124/1316	0.49 (0.35 to 0.69)*	112/1176	0.50 (0.35 to 0.70)*
Interstitial lung disease	32/94	3.15 (1.87 to 5.30)*	32/89	3.41 (2.01 to 5.80)*
Diabetes	59/196	1.89 (1.26 to 2.84)**	53/179	1.87 (1.22 to 2.87)**
Obesity**				
< 30	149/1475	1.00 (ref.)	135/1335	1.00 (ref.)
30–39.9	60/430	1.51 (1.01 to 2.27)***	53/387	1.47 (0.99 to 2.20)
≥ 40	13/68	3.05 (1.32 to 7.06)**	11/49	3.40 (1.52 to 7.61)**
Hypertension	117/476	1.82 (1.29 to 2.59)*	106/435	1.87 (1.29 to 2.70)**
Corticosteroids	133/564	2.61 (1.87 to 3.63)*	122/518	2.69 (1.90 to 3.82)
TNF blocker	17/563	0.46 (0.27 to 0.80)**	13/503	0.39 (0.21 to 0.73)**
Rituximab	32/111	2.76 (1.66 to 4.58)*	31/108	2.82 (1.68 to 4.72)*

CI: confidence interval; OR: odds ratio; TNF: tumor necrosis factor. Odds ratio was calculated using multivariable logistic regression models, using a backward stepwise selection method, with patients with mild or moderate infection as reference. Only variables selected by the model are presented. Full model included age, sex, interstitial lung disease, coronary heart diseases, diabetes, BMI, hypertension, chronic renal failure, disease history, corticosteroids, methotrexate, mycophenolate mofetil/mycophenolic acid, TNF blocker and rituximab. *n*/N indicated the number of events/number of cases.

[a] Odds ratio and *P*-value were calculated after multiple imputations (*m* = 10) to handle missing data.

* *P* < 0.001.

** *P* < 0.01.

*** *P* < 0.05.

https://doi.org/10.1016/j.jbspin.2023.105605

Table 2
Multivariable analyses for hospitalization status.

Variable	Imputed analysis[a] (n = 1973)		Available case analysis (n = 1771)	
	n/N	OR [95%CI]	n/N	OR [95%CI]
Age	644/1973	1.05 (1.04 to 1.06)*	575/1771	1.05 (1.04 to 1.06)*
Female gender	400/1316	0.66 (0.52 to 0.85)*	358/1176	0.66 (0.51 to 0.86)**
Interstitial lung disease	62/94	2.93 (1.76 to 4.87)*	60/89	3.17 (1.87 to 5.38)*
Coronary heart diseases	123/183	1.50 (1.01 to 2.23)	112/167	1.54 (1.02 to 2.33)***
Stroke	37/56	2.17 (1.14 to 4.13)***	32/50	2.12 (1.09 to 4.15)***
Diabetes	123/196	1.95 (1.34 to 2.83)*	111/179	1.85 (1.26 to 2.74)**
Obesity***				
< 30	456/1475	1.00 (ref.)	407/1335	1.00 (ref.)
30–39.9	158/430	1.28 (0.97 to 1.68)	143/387	1.30 (0.97 to 1.73)
≥ 40	30/68	2.18 (1.10 to 4.33)***	25/49	2.44 (1.26 to 4.74)**
Hypertension	264/475	1.49 (1.13 to 1.97)**	243/435	1.60 (1.20 to 2.14)**
Chronic renal failure	69/93	2.12 (1.20 to 3.75)***	62/85	1.95 (1.08 to 3.52)***
Corticosteroids	311/564	2.39 (1.87 to 3.06)*	280/518	2.29 (1.77 to 2.97)*
Hydroxychloroquine	61/181	1.57 (1.05 to 2.34)***	57/167	1.69 (1.11 to 2.57)***
TNFα blocker	86/563	0.56 (0.42 to 0.76)*	78/503	0.60 (0.44 to 0.82)**
Anti-IL6	12/75	0.22 (0.11 to 0.45)*	11/67	0.26 (0.12 to 0.54)*
Rituximab	70/111	2.89 (1.81 to 4.62)*	68/108	3.14 (1.95 to 5.06)*
Anti-IL1	9/15	4.89 (1.40 to 17.13)***	8/13	5.44 (1.40 to 21.22)***

BMI: body mass index; CI: confidence interval; OR: odds ratio; TNF: tumor necrosis factor. Odds ratio was calculated using multivariable logistic regression models, using a backward stepwise selection method, with outpatients as reference. Only variables selected by the model are presented. Full model included age, sex, interstitial lung disease, coronary heart diseases, stroke, diabetes, obesity, hypertension, cancer, chronic renal failure, disease history, corticosteroids, NSAIDs, hydroxychloroquine, leflunomide, mycophenolate mofetil/mycophenolic acid, azathioprine, anti-TNF, anti-IL6, rituximab and anti-IL1. n/N indicated the number of events/number of cases.

[a] Odds ratio and P-value were calculated after multiple imputations (m = 10) to handle missing data.

* $P < 0.001$.

** $P < 0.01$.

*** $P < 0.05$.

was associated with survival. Risks of hospitalization were similar (Tables S10 and S11).

Multivariable analyses for disease severity (Table 1) and hospitalization status (Table 2) identified age, frequency of interstitial lung disease, hypertension, BMI, use of corticosteroids or rituximab were associated with COVID-19 severity and increased risk of hospitalization. Being female and TNFα blocker use was protective of severe disease and lower risk of hospitalization ($P < 0.01$ for all), confirming initial results.

In our expanded cohort, we reaffirmed that age and comorbidities in patients with iRMD predicted COVID-19 severity and mortality throughout the waves of the COVID-19 pandemic in France. The profile of patients developing severe disease was unchanged after the first wave. Collectively, these data will aid physicians to make informed management decisions of COVID-19 risk in iRMD patients and reduce the frequency of COVID-19 disease severity. As such, these at-risk patients should still be eligible for booster vaccination, potential preventive treatments, and early antiviral treatment.

Funding

This study was not supported by research funding, but FAI^{2}R is funded by the French Ministry of Social Affairs and Health.

Research data availability statement

All relevant anonymized patient-level data is available upon reasonable request to the corresponding authors.

Disclosure of interest

CR received consulting fees from AbbVie, Astra Zeneca, GSK, Novartis, Pfizer, honoraria from AbbVie, Amgen, Astra Zeneca, GSK, Pfizer, Biogen, BMS, Galapagos, Lilly, travel support from Amgen, Celltrion, Galapagos, patents planned, issued or pending by Astra Zeneca, and receipt of equipment, materials, drugs, medical writing, gifts or other services by Biogen and Lilly, all unrelated to this manuscript.

EH received Speakers fees from Johnson & Johnson, GlaxoSmithKline, Roche-Chugai, Otsuka; and research funding from CSL Behring, GlaxoSmithKline, Johnson & Johnson, Roche-Chugai, Consultant of: Bayer, Boehringer Ingelheim, GlaxoSmithKline, Johnson & Johnson, Roche-Chugai, Sanofi-Genzyme, Novartis, grant/research support from: GlaxoSmithKline, Roche-Chugai, Sanofi-Genzyme, Sobi, Novartis, all unrelated to this manuscript.

TP received consulting fees from Abbvie, Amgen, Biogen, BMS, Celgene, Celltrion, Fresenius-Kabi, Galapagos, Janssen, Lilly, MSD, Nordic, Novartis, Pfizer, Roche-Chugai, Sandoz, Sanofi, UCB, all unrelated to this manuscript.

TT has received consultancy/speaker's fees from Amgen, Arrow, Biogen, Chugai, Expanscience, Grunenthal, Jansen, LCA, Lilly, MSD, Nordic, Novartis, Pfizer, Sanofi, Thuasne, Theramex, TEVA and UCB and financial support or fees for research activities from: Bone Therapeutics, Chugai, UCB, all unrelated to this manuscript.

HM TT has received consultancy/speaker's fees from Amgen, AbbVie, Arrow, Biogen, Chugai, Celltrion healthcare, Jansen, Lilly, MSD, Medac, Nordic, Novartis, Pfizer, Sanofi-Genzyme, and UCB and financial support or fees for research activities from: Pfizer, Sanofi-Genzyme, Celltrion healthcare, and Gebro, all unrelated to this manuscript.

Acknowledgments

Muriel Herasse (Filière des maladies auto-immunes et auto-inflammatoires rares [FAI^{2}R], CHU de Lyon, Lyon, France) had a major role in collecting the missing data of the cohort. We thank Julien Labreuche (biostatistician at CHU of Lille, Lille, France) for the help in the statistical analysis. We thank the pro-bono support of SANOÏA Digital Contact Research Organization (Aubagne, France) team, who provided outstanding electronic case report forms, agile data visualization, and extensive project support. JetPub Scientific Communications LLC, supported by AFORMI and CRI, assisted in the preparation of this manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2023.105605.

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Elodie Drumez[a,1]
Christophe Richez[b,1,*]
Louis Bebear[c]
Muriel Herasse[d]
René-Marc Flipo[e]
Hubert Marotte[f]
Sophie Georgin-Lavialle[g,h]
Raphaèle Seror[i]
Edouard Pertuiset[j]
Jérôme Avouac[k]
Pascal Chazerain[l]
Nicolas Roux[m]
Thao Pham[n]
Emmanuelle Dernis[o]
Yurdagul Uzunhan[p]
Amélie Servettaz[q]
Soumaya El Mahou[r]
Patrice Cacoub[s]
Mohamed Hamidou[t]
Bruno Fautrel[u]
Thierry Thomas[v]
Eric Hachulla[w], on Consortium[2] contributors[3],

[a] *Department of Biostatistics, CHU of Lille, Lille, Hauts-de-France, France*
[b] *CNRS, ImmunoConcEpT, UMR 5164, Department of Rheumatology, University of Bordeaux, CHU of Bordeaux, 33000 Bordeaux, France*
[c] *Department of Rheumatology, CHU of Bordeaux, 33000 Bordeaux, France*
[d] *Filière des maladies auto-immunes et auto-inflammatoires rares, hôpital Huriez, centre hospitalier universitaire de Lille, Lille, France*
[e] *Service de rhumatologie, université de Lille, CHU de Lille, Lille, France*
[f] *Inserm, SAINBIOSE U1059, service de rhumatologie, Mines Saint-Étienne, université Jean-Monnet Saint-Étienne, CHU de Saint-Étienne, 42023 Saint-Étienne, France*
[g] *Internal Medicine Department, Tenon Hospital, Sorbonne University, AP–HP, 4, rue de la Chine, 75020 Paris, France*
[h] *National Reference Center for Autoinflammatory Diseases and AA Amyloidosis (CEREMAIA), Tenon Hospital, Paris, France*
[i] *Inserm UMR 1184, service de rhumatologie, Centre de référence des maladies auto-immunes systémiques rares, hôpital Bicêtre, université Paris-Saclay, Assistance publique–Hôpitaux de Paris (AP–HP), Le Kremlin-Bicêtre, France*
[j] *Service de rhumatologie, centre hospitalier René-Dubos, Pontoise, France*
[k] *Service de rhumatologie, hôpital Cochin, centre université de Paris Cité, université de Paris, Assistance publique–Hôpitaux de Paris, Paris, France*
[l] *Internal Medicine and Rheumatology Department, Groupe Hospitalier Diaconesses Croix Saint-Simon, 75020 Paris, France*
[m] *Rheumatology department, Hôpitaux Privés de Metz – Hôpital Robert-Schuman, Metz, France*
[n] *Department of Rheumatology, Sainte-Marguerite Hospital, Aix-Marseille University, AP–HM, Marseille, France*
[o] *Department of Rheumatology and Clinical Immunology, General Hospital, Le Mans, France*
[p] *Inserm UMR 1272, Department of Respiratory Medicine, Reference Center for Rare Pulmonary Diseases, Hôpital Avicenne, Université Sorbonne Paris Nord, AP–HP, Bobigny, France*
[q] *Service de médecine interne, maladies infectieuses et immunologie clinique, hôpital Robert-Debré, CHU de Reims, Reims, France*
[r] *Service de rhumatologie, centre hospitalier de Dron, 59200 Tourcoing, France*
[s] *UMR 959, Department of Internal Medicine and Clinical Immunology, Centre de Référence des Maladies Auto-Immunes Systémiques Rares, Pitié-Salpêtrière Hospital, Sorbonne Université, 75013 Paris, France*
[t] *Service de médecine interne, PHU3, centre hospitalier universitaire de Nantes – Hôtel-Dieu, 1, place Alexis-Ricordeau, 44093 Nantes, France*
[u] *Inserm UMRS 1136, département de rhumatologie, hôpital Pitié-Salpêtrière, Institut Pierre-Louis d'épidémiologie et de santé publique, Sorbonne université, AP–HP, 75013 Paris, France*
[v] *Inserm, SAINBIOSE U1059, service de rhumatologie, université Jean-Monnet Saint-Étienne, CHU de Saint-Étienne, 42023 Saint-Étienne, France*
[w] *Department of Internal Medicine and Clinical immunology, Referral Centre for Rare Systemic Auto-immune Diseases North and North-West of France, Lille University School of Medicine, Lille, France*

[*] Corresponding author. CNRS, ImmunoConcEpT, UMR 5164, Department of Rheumatology, University of Bordeaux, CHU of Bordeaux, 33000 Bordeaux, France.
E-mail addresses: christophe.richez@chu-bordeaux.fr, christophe.richez@mac.com (C. Richez)

[1] These authors contributed equally to this work.

[2] FAI[2]R: Filière des maladies auto-immunes et auto-inflammatoires rares; SFR: Société française de rhumatologie; SNFMI: Société nationale française de médecine interne; SOFREMIP: Société francophone pour l'étude des rhumatismes et maladies inflammatoires pédiatriques; CRI: Club

rhumatismes et inflammation; IMIDIATE: Immune-Mediated Inflammatory Disease Alliance for Translational and Clinical Research Network.

[3] Contributors in alphabetical order are: Aeschlimann Florence, Paris; Agard Christian, Nantes; Ait-Abdallah Nassim, Paris; Albert Jean-David, Rennes; Alcais Didier, Le Havre; Allain Jean-Sébastien, Rennes; Allanore Yannick, Paris; Amoura Zahir, Paris; Amouzougan Adamah, Saint-Priest-en-Jarez; Andre Emma, Paris; Arbault Anaïs, Dijon; Arlet Jean-Benoît, Paris; Arnaud Laurent, Strasbourg; Arniaud Denis, Marseille; Arty-Hue Herliette, Gap; Atlan Lucie, Amboise; Aubin François, Besançon; Audemard-Verger Alexandra, Tours; Audoin-Pajot Christine, Toulouse; Audren Victor, Paris; Avenel Gilles, Rouen; Avouac Jérôme, Paris; Bach-Bunner Maxime, Colmar; Bacquet-Deschryver Hélène, Dieppe; Bader-Meunier Brigitte, Paris; Balandraud Nathalie, Marseille; Balblanc Jean-Charles, Trevenans; Ballot-Schmit Claire, Besançon; Bally Stéphane, Chambery; Banal Frédéric, Saint-Mandé; Banneville Béatrice, Paris; Barbery Pierre, Lisieux; Bart Géraldine, Rennes; Basch André, Caluire-et-Cuire; Baumier Vincent, Clermont-Ferrand; Bayer Guillaume, Quincy-sous-Senart; Bayle Sophie, Avignon; Beauvais Catherine, Paris; Beinat Rudie, Bordeaux; Belin Véronique, Thonon-les-Bains; Belkhir Rakiba, Kremlin-Bicêtre; Belot Alexandre, Bron; Beltai Auriélie, Narbonne; Benainous Ruben, Bobigny; Benammar Mohammed, Saint-Quentin; Bendahmane Chahinez, Pontoise; Benhamou Mathilde, Versailles; Benhamou Ygal, Rouen; Benmansour Ahmed, Chateauroux; Bennet Pascal, Bois-Guillaume; Bernoux-Manat Brigitte, Rennes; Berthet Elise, Clermont-Ferrand; Berthier Sabine, Dijon; Berthoud Olivia, Rennes; Berthoux Emilie, Lyon; Bertolini Ewa, Annecy; Bigot Adrien, Tours; Bisson-Vaivre Aurélia, Castres; Blaison Gilles, Colmar; Bolla Gilles, Cannes; Bonidan Olivier, Agen; Bonnet Christine, Limoges; Borie Raphaël, Paris; Borocco Charlotte, Kremlin-Bicêtre; Bossert Marie, Trevenans; Boudou Laurence, Saint-Chamond; Bouhour Françoise, Bron; Bouiller Kévin, Besançon; Bouillet Laurence, Grenoble; Bouldoires Bastien, Colmar; Bourree Thomas, Cholet; Boussen Ines, Paris; Boussoualim Karima, Saint-Priest-en-Jarez; Bouvard Eric, Paris; Brondino Régine, Marseille; Buchlin Pierre, Mulhouse; Cabantous Laurence, Merignac; Cacoub Patrice, Paris; Cadiou Simon, Rennes; Cantagrel Alaine, Toulouse; Caplanne Didier, Bayonne; Carbasse Aurélia, Montpellier; Carteni Maurizio, Saint-Pierre-de-Coutances; Castel Brice, Tarbes; Cathebras Pascal, Saint-Priest-en-Jarez; Caumont Hervé, Troyes; Cayot-Bouillet Audrey, Dijon; Celant Annalisa, Metz; Cerf Payrastre Isabelle, Pontoise; Chaffin Aurélie, Avranches; Chaigne Benjamin, Paris; Chaillous Benoît, Herbiers; Champy Romuald, Écuelles; Charcot Agnès, Paris; Charles Pierre, Paris; Charpin Caroline, Marseille; Chatelus Emmanuel, Strasbourg; Chaudier Bernard, Marseille; Chazerain Pascal, Paris; Chertok Pascale, Argenteuil; Chevalier Xavier, Créteil; Chevreau Maxime, Aix-les-Bains; Chotard Emilie, Paris; Chu Miow Lin Delphine, Tours; Claudepierre Pascal, Créteil; Clavel Gaëlle, Paris; Clavel-Osorio Cyril, Saint-Martin; Clay Marine, Grenoble; Clet Johanna, Bordeaux; Coassy Astrid, Saint-Priest-en-Jarez; Cohen Fleur, Paris; Cohen Gregory, Avignon; Colette-Cedoz Marie-Eve, Bourgoin-Jallieu; Collercandy Nived, Tours; Colombey Antoine, Saint-Nazaire; Comarmond Chloé, Paris; Combe Bernard, Montpellier; Comparon Céline, Bobigny; Constant Elodie, Valence; Constantin Arnaud, Toulouse; Coquerelle Pascal, Beuvry; Corli Justine, Douai; Corre Clémence, Vannes; Costedoat-Chalumeau Nathalie, Paris; Couderc Marion, Clermont-Ferrand; Couret Marie, Bourg-en-Bresse; Courvoisier Natacha, Nogent-sur-Marne; Coury-Lucas Fabienne, Pierre-Bénite; Coutarel Cécile, Clermont-Ferrand; Coutier Fabrice, Vesoul; Damade Richard, Chartres; Daver-Malaterre Laurence, Marseille; De Moreuil Claire, Brest; Decrock Marijke, Perpignan; Delahousse Michel, Suresnes; Delattre Barrois Emilie, Quingey; Deligny Christophe, Fort-de-France; Denarie Delphine, Roanne; Denis Amélie, Le Mans; Deprouw Camille, Courbevoie; Dernis Emanuelle, Le Mans; Deroux Alban, Grenoble; Desbarbieux Renaud, Boulogne-sur-Mer; Descamps Elise, Paris; Desdoits Alexandra, Caen; Deslandre Chantal, Paris; Desmurs Marie, Mulhouse; Despaux Jacques, Montelimar; Desplats Marie, Lambersart; Detree Frédérick, Reims; Devauchelle-Pensec Valérie, Brest; Devaux Mathilde, Poissy; Dhote Robin, Bobigny; Diaz Harmonie, Narbonne; Dieude Philippe, Paris; Dieudonne Yannick, Strasbourg; Diot Elisabeth, Tours; Direz Guillaume, Le Mans; Djeddi Djamal-Dine, Amiens; Domont Fanny, Paris; Douvier Sarah, Aix-les-Bains; Drouet Béatrice, Pau; Dubost Jean-Jacques, Clermont-Ferrand; Duc Catherine, Romans-sur-Isère; Ducornet Angélique, Saint-Brieuc; Dufauret-Lombard Carine, Limoges; Dumaine Cécile, Paris; Dumel Anne-Elisabeth, Cernay; Dumoulin-Richez Chantal, Merignac; Duquesne Agnès, Bron; Durand Géraldine, Poitiers; Durandin-Truffinet Mariane, Paris; Duret Pierre-Marie, Colmar; Durieux-Mehlman Stéphanie, Saint-Cloud; Dusser-Benesty Perrine, Kremlin-Bicêtre; Duval Maïka, Antibes; Ebbo Mikaël, Marseille; Ebstein Esther, Paris; Economu-Dubosc Andra, Sucy-en-Brie; El Mahou Soumaya, Tourcoing; Emilie Stéphanie, Villeneuve-Saint-Georges; Euvrard Romain, Bourg-en-Bresse; Evon Philippe, Bar-le-Duc; Eymard-Gibert Claire, Lyon; Fabre Sylvie, Montpellier; Fagedet Dorothée, Gap; Farge-Bancel Dominique, Paris; Farhat Meryem, Lille; Fauconier Marion, Reims; Fautrel Bruno, Paris; Fechtenbaum Jacques, Pantin; Felten Renaud, Strasbourg; Ferreira-Maldent Nicole, Tours; Feurer Elodie, Lyon; Fichet Amandine, Trevenans; Flaisler Françoise, Nîmes; Flipo René-Marc, Lille; Florens Nans, Lyon; Foltz Violaine, Paris; Fontanges Elisabeth, Lyon; Foret Jennifer, Dax; Fougerousse Anne-Claire, Saint-Mandé; Fouque-Aubert Anne, Lyon; Foutrier-Morello Catherine, Plan-de-Cuques; Francois-Pradier Hélène, Paris; Frantzen Léa, Mulhouse; Fremond Marie-Louise, Paris; Fritz

Pierre, Paris; Froissart Antoine, Créteil; Fulpin Jean, Toulon; Fuzibet Piera, Orléans; Gaches Francis, Toulouse; Gagneux-Lemoussu Laurence, Reims; Gahier Penhoat Mélanie, Saint-Nazaire; Galland Joris, Paris; Gandjbakhch Frédérique, Paris; Gardette Anaïs, Vichy; Garnier Nicole, Plaisance-du-Touch; Garraud Thomas, Nantes; Garrot Jean-François, Semur-en-Auxois; Gastaldi Romain, Grenoble; Gaudin Philippe, Grenoble; Gaud-Listrat Véronique, Saint-Michel-sur-Orge; Gauthier-Prieur Maud, Louviers; Gauzere Loraine, Saint-Denis; Geoffroy Marion, Reims; Georgescu Dana, Vienne; Georgin-Lavialle Sophie, Paris; Gerard Nathalie, Dijon; Gerber Anne, Saint-Denis; Gervais Elisabeth, Poitiers; Gibert Christelle, Valence; Gibert Eric, Paris; Gill Ghislaine, Paris; Gillard Jérôme, Lons-le-Saunier; Gilson Mélanie, Grenoble; Gimonnet Pauline, Épernay; Giraudet-Le Quintrec Jeanine-Sophie, Paris; Giraud-Morelet Aude, Écully; Glace Baptiste, Vichy; Glanowski Camille, Saint-Mandé; Godeau Bertrand, Créteil; Gombert Bruno, La Rochelle; 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How Shing Koy Elsa, Saint-Priest-en-Jarez; Hua Charlotte, Nîmes; Hudry Christophe, Paris; Huguenel Serge, Sarrebourg; Jaccard Clara, Clermont-Ferrand; Jacquemier Jean-Michel, Cornebarrieu; Jamard Bénédicte, Toulouse; Jan Catherine, Bar-le-Duc; Jean Sylvie, Rennes; Joffres Laurie, Saint-Benoît; Jousse-Joulin Sandrine, Brest; Jouvray Mathieu, Arras; Juge Pierre-Antoine, Paris; Juillard Laurent, Lyon; Jullien Denis, Lyon; Kabchou Abdelkrim, Vichy; Karkowski Ludovic, Lyon; Karman Françoise, Pontault-Combault; Kemiche Farid, Pontoise; Keraen Jérémy, Quimper; Kieffer Pierre, Mulhouse; Kone-Paut Isabelle, Kremlin-Bicêtre; Koreichi Abdeldajallil, Lorient; Kostine Marie, Bordeaux; Krebs Stéphanie, Ploemeur; La Batide Alanore Sylvain, Paris; Lacombe Valentin, Angers; Lafforgue Pierre, Marseille; Lahalle Sophie, Paris; Lambert Marc, Lille; Lambrecht Isabelle, Reims; Lamer François, Rennes; Langlois Vincent, Le Havre; Lanot Sylvain, Alençon; Lanteri Aurélia, Antibes; Larbre Jean-Paul, Pierre-Bénite; Latourte Augustin, Paris; Lavigne Christian, Angers; Le Gouellec Noémie, Valenciennes; Le Guen Guegan Sophie, Contamine-sur-Arve; Le Guenno Guillaume, Clermont-Ferrand; Lebrun Agnès, Paris; Ledoult Emmanuel, Tourcoing; Legoupil Nathalie, Paris; Legrand Erick, Angers; Leguy Diane, Roubaix; Leguy-Seguin Vanessa, Dijon; Leloire Olivier, Ronchin; Leroux Christophe, Dreux; Leroy Rémi, Dunkerque; Leroy-Gouix Marie, Vannes; Leske Charles, Cholet; Leturcq Tifenn, Paris; Leurs Amélie, Dunkerque; Leveque-Michaud Céline, Valence; Limbach François-Xavier, Saverne; Liote Frédéric, Paris; Lohse Anne, Trevenans; Lozac'h Pierre, Le Mans; Lucas Charlotte, Rennes; Mabrut Etienne, Pierre-Bénite; Madelon Aurélie, Grenoble; Magnol Marion, Toulouse; Magy-Bertrand Nadine, Besançon; Mahevas Matthieu, Créteil; Maillard Hélène, Lille; Maillet Thibault, Macon; Maillot François, Tours; Malochet-Guinamand Sandrine, Clermont-Ferrand; Mangon Quentin, Aurillac; Mankikian Julie, Tours; Marchou-Lopez Sylvie, Crolles; Margarit Nathalie, Portet-sur-Garonne; 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Queyrel Viviane, Nice; Raffray Loïc, Saint-Denis; Razanamahery

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Accepted 21 June 2023